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(54) Title: METHOD OF ENHANCING NUTRITIONAL VALUE OF COLOSTRUM AND FIRST MILK OF PREGNANT MAMMALS

(57) Abstract

A method is provided for increasing the nutritional value of colustrum and first milk of pregnant mammals. $\beta$-hydroxy-$\beta$-methylbutyric acid (HMB) was orally administered for several days prior to the birth of the offspring. Administered at an effective level, fat content was increased of the colostrum and first milk.

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# METHOD OF ENHANCING NUTRITIONAL VALUE OF COLOSTRUM AND FIRST MILK OF PREGNANT MAMMALS

## FIELD OF INVENTION

This invention relates generally to the feeding of mammals to stimulate lactation and to improve milk quality. The invention is particularly concerned with dietary additives for nursing domestic mammals which can enhance nutritional value of the milk and thereby benefit the nursing offspring.

## BACKGROUND OF INVENTION

In the raising of domestic mammals, such as cattle and swine, newly born animals are usually permitted to nurse on the mother's milk for at least several weeks. Baby animals immediately after birth thereby receive the colostrum and the milk as their complete diet. It is well recognized that improving the nutritional value of the colostrum and milk would be beneficial to the offspring. Increasing the fat content of the milk is believed to be of particular value, and it would be especially desirable to achieve increased fat together with increased protein.

The need for improving the nutritional value of the colostrum and milk is particularly acute with respect to raising of pigs. Immediately following birth baby pigs are in a nutritionally vulnerable condition which frequently results in the death of some of the pigs in a litter. If the quality and quantity of the available milk from the nursing sow could be appreciably improved, this would be of great benefit to the nursing piglets, increasing rate of weight gain and chances for survival.

Published European Patent Application 0 225 165 recognizes the problem discussed above with particular reference to pigs. The disclosure proposes to administer phenethanol amines to increase the fat content of sow's milk. A representative phenethanol amine is 1-(4-hydroxy-phenyl)-2-[3-(4-hydroxyphenyl)-1-methyl-propylamino] ethanol, which may be administered orally or percutaneously from about three days prior to farrowing to about ten days after farrowing.

Administration of synthetic organic compounds to domestic animals may present a health hazard to people eating the meat and drinking the milk of the animals. Use of such methods with domestic animals is therefore very carefully controlled by the Food and Drug Administration. It would be preferable from the standpoint of commercial utilization to find an ordinary nutrient or metabolite which can be used as a feed additive to increase the fat and/or protein contents of the milk of nursing domestic mammals.

It has been reported that leucine supplementation of the diets of lactating mammals can increase milk production: Chugh et al. (1989), Nutr. Res., 9:233-236; and Shanker et al. (1985), Nutr. Res., 5:1353-1358. Both reports involved the addition of the essential amino acid L-leucine to the diets of pregnant rats during gestation and lactation. Chugh et al. used an experimental diet containing about 50 grams of L-leucine per kilogram of feed. The rats receiving the leucine-supplemented diet lost weight as compared with the control rats, but their milk yield was increased and their nursing offspring achieved higher weights than the controls.

Shanker et al. previously had reported similar results. The body weights of the female rats receiving the added leucine were reduced, but there was an increase in lactational performance and in the growth rates of the baby rats. Neither Chugh et al. or Shanker et al. reported an increase in the protein content of the milk from the leucine-supplemented rats.

As far as is known, it has not been experimentally demonstrated that the lactation effects produced in rats, as described above, can be obtained with larger domestic mammals like swine and cattle. However, one report has been published in which lactating sows were fed a diet supplemented with leucine: Rousselow et al. (1979), J. Anim. Sci. 49:498-506. L-leucine supplementation of feeds for lactating sows was tested at leucine levels from 0.64 to 1.24 percent of the diet in two separate trials. In only one of the two trials an increase in milk production was observed from the leucine supplementation. The rates of weight gain of the suckling pigs were not improved in either test, and no increase in protein content was reported.

The keto acid analog of L-leucine is alpha-ketoisocaproate (KIC), which is sometimes referred to as "keto-leucine", and does not have L and D forms. It is known that there is a conversion of plasma circulating leucine to KIC. Published studies have shown that KIC can be substituted in animal diets for L-leucine providing that much larger molar amounts of KIC are used: Chawla et al. (1975), J. Nutr. 105:798-803; and Boebel and Baker (1982), J. Nutr., 112:1929-1939.

It is also known that the addition of KIC to the diets of lactating domestic mammals can improve the quantity and quality of the milk produced. [See, Nissen U.S. Patent 4,758,593; and Vandehaar et al. (1988), J. Dairy Sci., 71:3352-3361.] In experiments with cows and goats, KIC supplementation during lactation increased milk yield and milk fat. No improvement in milk protein was reported.

As described in U.S. Patent 4,760,090 KIC can be fed to cattle and sheep for enhancement of growth and feed efficiency. In another application of KIC feeding, egg production of laying chickens was increased (U.S. Patent 4,764,531).

In recent experiments carried out by Dr. Steven L. Nissen at Iowa State University, Ames, Iowa, β-hydroxy-β-methylbutyric acid (HMB) was fed to domestic animals. The effects obtained were different than with KIC. It was found that metabolically KIC and HMB are not intra-convertible. KIC is the direct metabolic product of leucine, while HMB is only a minor metabolite in the complex leucine/KIC metabolic cascade. Differing biological activities of HMB when fed to domestic mammals is the basis for U.S. Patent 4,992,470, which describes the administration of HMB to enhance the immune response of mammals, and U.S. Patents 5,087,472 and 5,028,440 relate to the feeding of HMB to meat producing animals (ruminants and poultry) to increase selectively the development of lean tissues.

The biological mechanism by which leucine stimulates lactation has not been elucidated. It is known that leucine is one of the essential amino acids that is taken up by the mammary gland in excess of the

quantity needed for milk protein synthesis [See, Wohlt et al. (1977) J. Dairy Sci., 12:1875- 1882.] As shown by Wohlt et al., in lactating cows approximately 30 grams of leucine is removed per day from the plasma in excess of that needed for milk protein synthesis. This suggests that L-leucine has some unknown additional function in the mammary glands. Leucine can be provided as an amino acid component of natural feed materials, such as corn and soybean meal. However, the amount of leucine in diets is usually from about 6 to 20% of the protein (w/w) or from 0.8 to 2% of the complete diet. On the basis of experiments with rats, as cited above (Chugh et al. 1989), the amount of leucine in the diet would need to be increased to as much as 5% of the diet to achieve the milk fat increases observed in rats. Such large leucine supplementation of diets for nursing domestic animals is not commercially practical.

As far as it is known, there have been no reports of experiments in which HMB has been administered to lactating domestic mammals and the lactation effects observed. It is therefore not known to what extent or in what way HMB can be used to improve the quantity or quality of the milk of nursing mammals.

## SUMMARY OF INVENTION

This invention is based on the discovery that the administration of HMB to pregnant domestic mammals when carried out immediately prior to parturition can dramatically enhance the nutritional value of the colostrum and first milk. In an experiment with pregnant sows, the colostrum and milk collected during the first day after farrowing contained nearly 40% more milk fat after HMB administration for three days

prior to farrowing. Test results also indicate that the protein content of the milk of HMB-treated pregnant sows can be significantly increased. Moreover, the test data indicates that the rate of weight gain of the suckling pigs during the first one to three weeks can be appreciably increased so that the pigs at weaning will have a greater weight than pigs nursing on milk from control sows. A reduction in mortality of the baby pigs should therefore be a further benefit.

The method of the present invention is believed to be applicable to the raising of domestic mammals generally for enhancing the nutritional value of colostrum and first milk, and thereby improving the growth rate and health of the offspring. Specifically, the method is expected to be beneficial in raising cattle, sheep, goats, horses, dogs and cats. From an economic standpoint, however, the method is expected to have importance in the raising of meat-producing animals, such as hogs, beef cattle, and sheep.

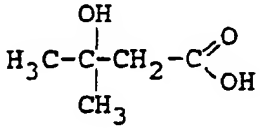
In practicing the method of this invention, the HMB should be administered to the pregnant mammals for at least 48 hours prior to parturition. The preferred embodiments, HMB is administered for 5 to 10 24-hour days prior to parturition. This pre-birthing treatment appears to be essential for obtaining a large increase in the milk fat of the colostrum and the first milk. The administration of the HMB can be continued for several days after the start of milk production. It is preferred to continue the HMB administration for 24 to 72 hours following parturition, and some additional benefit to the nutritional value of the milk can be obtained by

continuing the HMB administration until the baby mammals are weaned.

DETAILED DESCRIPTION

The base compound for practicing the present invention is β-hydroxy-β-methylbutyric acid (HMB). It can be used in its free acid form or as an edible salt. Other edible derivatives of HMB which convert directly in the body to HMB can be used.

The free acid compound is also called β-hydroxy- isovaleric acid, and has the following structure:



It is preferred to administer HMB as an edible salt, ester, or lactone. The calcium salt is especially convenient because it is less hydroscopic than the sodium or potassium salts, although these can also be used. Esters of HMB such as particularly the methyl or ethyl esters are alternative forms. Such esters are rapidly converted in the body to free acid HMB. For administration as a lactone, the compound isovalaryl lactone can be used. This compound and similar lactones are rapidly converted in the body to free acid HMB.

The free acid form can be designated as "HMB-acid", and the salt forms, such as the calcium, sodium, potassium or magnesium salts, respectively, as "Ca-HMB", "Na-HMB", "K-HMB", and "Mg-HMB". Correspondingly, the esters can be designated "HMB-methyl ester", "HMB-ethyl ester", etc. The lactone can be designated "HMB-lactone". HMB has no

steroisomers and accordingly does not exist in L or D forms.

HMB is not commercially available at this time. However, procedures are known for synthesizing this compound from commercially available starting materials. For example, HMB can be synthesized by oxidation of diacetone alcohol (4-hydroxy-4-methyl-2-pentanone). A suitable synthesis procedure is described by Coffman, et al., J. Am. Chem. Soc., 80:2882-2887, at 2885 (1958). As there described, β-hydroxy-isovaleric acid (HMB) is prepared by an alkaline sodium hypochlorite oxidation of diacetone alcohol. The product is recovered in free acid form which can be converted to the desired salt. For example, HMB can be prepared as its calcium salt (Ca-HMB) by a similar procedure to that of Coffman, et al. in which the HMB acid obtained is neutralized with calcium hydroxide, and recovered by crystallization from an aqueous ethanol solution. For example, a 95% ethanol solution can be used with the Ca-HMB at about a 10% concentration.

Since Ca-HMB is a preferred form for administering HMB, the dosage amount of HMB can be expressed in terms of corresponding molar amount of Ca-HMB. On a Ca-HMB basis, the HMB compound should be orally administered in amounts from 0.5 to 100 milligrams per kilogram of body weight per 24 hours which are effective to increase the milk fat in the colostrum and first milk. The most critical time for administration of the HMB compound appears to be during the 24 to 72 hours immediately before birth of the offspring. The administration of the HMB compound during that time will greatly increase the fat content of the colostrum and first milk.

The term "first milk" as used herein is intended to refer to the milk produced during the first 24 hours after parturition, which period will also include release of the colostrum.

Exact proportioning of the administered HMB compound in relation to body weight is not essential. For practical feeding purposes, the amount to be fed can be based on grams of Ca-HMB per 24 hours per animal. For example, the following table illustrates recommended feeding levels for important domestic mammals. The method should also be useful with pregnant women, the amounts to be used being from about 0.5 to 10 grams (Ca-HMB basis) per 24 hours.

TABLE A

Recommended Feeding Levels for HMB

| Animal | Grams/24 hour (Ca-HMB basis) Range | Preferred |
|---|---|---|
| Swine (sows) | 1-10g | 4g |
| Cattle (cows) | 2-30g | 8g |
| Sheep (ewes) | .2-5g | 1g |
| Dogs | 10-2000mg | 0.2g (0.1-0.5g)* |
| Cats | 5-1000mg | .1g (0.05-0.25g) |

Depending on weight.

In a preferred embodiment, the HMB compound is orally administered to the pregnant mammals, such as by incorporation in feeds, for 72 hours before birth of the offspring, and the feeding is continued for 24 to 48 hours after birthing. The feeding levels set out in Table A are recommended for these time periods.

By feeding the HMB compound for as short a time as 48 hours prior to parturition, the fat content of the colostrum and first milk can be greatly

increased and the protein content can also be enhanced. Thus, the nutritional value of the first liquid feed received by the baby mammals is higher than that of the milk they would normally receive. This "head-start" can result in increased rates of weight gain of the offspring, resulting in healthier young animals, and probably a lowered mortality.

The method of this invention is applicable to the raising of meat-producing animals, such as principally hogs, cattle and sheep. However, the method can also be advantageously used with other domestic mammals, including goats, horses, and animal pets such as dogs and cats. With respect to all of these species, it is desirable to produce the strongest, healthiest, and fastest growing offspring. For increasing the quantity of milk produced a longer time of HMB feeding prior to birth of the offspring may be desirable. For example, feeding an HMB compound to the pregnant mammals for 30 to 60 days before birth of the offspring may result in an increase in the total volume of milk produced. Such an increase can be due to the effect of the HMB in causing growth and enlargement of the mammary glands.

Within 24 to 48 hours after birth of the mammals, the enhanced fat and protein of the milk will begin to decline. However, it appears from the experimental data that some benefit with respect to higher fat and protein content may be obtainable by continuing feeding of the HMB compound until the baby mammals are weaned. For example, with respect to baby pigs, a preferred embodiment of the method of this invention, feeding of the nursing sows benefically can be continued for the normal time for weaning the piglets (at about 3 weeks).

The HMB compound can be administered by admixing it with the feed for the pregnant mammals. An HMB compound in the form of a powder can be intermixed with a complete feed ration, feed concentrate, or other dry feed material being given to the pregnant mammals. Alternatively, although not as desirably, a water-soluble HMB compound, such as the sodium salt of HMB (Na-HMB) can be dissolved in the drinking water for the pregnant mammals. With that route of administration, it may be more difficult to control the amount of HMB administered.

In the United States lactation rations for domestic mammals, such as hogs, cattle and sheep, frequently contain a major proportion of ground corn, soybean meal, or mixtures of ground corn and soybean meal. Such rations, typically contain from about 6 to 20 weight percent of leucine on a total protein basis. While rations containing a greater percent of leucine can be used, they are not necessary in following the method of the present invention. HMB not leucine is the active component which provides the nutritionally improved milk.

This invention and the results obtainable thereby are further illustrated by the following experimental examples.

Experiments 1 to 3

The experiments were carried out with pregnant sows. The HMB compound (Ca-HMB) in the form of a powder was mixed uniformly with a complete lactation ration. The experimental ration for Experiments 1 and 2 contained 15.6% protein and about 1.5% leucine based on the total protein, and was formulated as set out below. The Experiment 3 feed

ration contained the ingredients set out below, and was also estimated to contain approximately 1.5% leucine based on the total protein which was about 16.9%.

Experimental Ration for Experiments 1 and 2

| Formula | | Composition on Dry Matter Basis | |
|---|---|---|---|
| Corn | 68.96% | Dry Matter | 87.2% |
| SBM | 22.05% | Crude protein | 15.6% |
| Dicalcium | | Fat | 6.6% |
| Phosphate | 2.47% | Fiber | 2.6 |
| Ca Carbonate | 1.0% | Calcium | 1.08% |
| Min/Vit | 1.05% | Phosphorus | 0.87% |
| Salt | 0.5% | Metabolizable | |
| Treatment | 0.03% | Energy (Kcal/kg) | 360 |

Experimental Ration for Experiment 3

| Formula | | Composition on Dry Matter Basis | |
|---|---|---|---|
| Corn | 74.35% | Dry Matter | 88.1% |
| SBM (50%) | 20.6% | Crude protein | 16.9% |
| Dicalcium | | Fat | 2.86% |
| Phosphate | 2.47% | Fiber | 2.3 |
| Ca Carbonate | 1.0% | Calcium | 1.08% |
| Min/Vit | 1.05% | Phosphorus | 0.87% |
| Salt | 0.5% | Metabolizable | |
| Treatment | 0.03% | Energy (Kcal/kg) | 360 |

The following is a summary of data obtained from sows fed approximately 2 grams of Ca-HMB per 24 hours. The HMB was fed when sows entered the farrowing crate (approximately 2 days prior to farrowing), and was fed continuously until weaning of the pigs at 3 weeks of age.

The least square means represent data obtained from the three separate experiments: Experiment 1 (6 pairs of sows), Experiment 2 (19 pairs of sows); and Experiment 3 (10 pairs of sows). The diets fed met or exceeded NRC recommendations for lactation rations and were based on corn and soybean meal. Back fat was measured by ultrasound probe. Sow weights were taken before birth and after weaning. Milk was collected at the ends of days (24 hour periods) 1, 10 and 21 of lactation. The day 1 collections included the colostrum. For the last two collections oxytocin injection as used to aid in milk sampling. Days to pregnant were calculated from subsequent birth data, and subsequent litter weights were obtained on each sow.

Table B

Effect of Feeding 2g of Calcium-HMB
to Sows and Resulting Piglet Performance

| | Cont | Treat | P< Treat | P< Treat X exp |
|---|---|---|---|---|
| Number of sows | 34 | 34 | | |
| Parity | 3.25 | 3.14 | | |
| Sow weight (lbs.) | 453 | 456 | 0.74 | 0.62 |
| Sow loss (lbs.) | -24.5 | -35.7 | 0.10 | 0.23 |
| Back fat loss (mm) | -0.63 | -2.19 | 0.02 | 0.39 |
| Initial pig no. | 10.5 | 10.0 | 0.21 | 0.55 |
| Wt/pig birth (lbs.) | 3.24 | 3.36 | .10 | 0.05 |
| Death loss (No/lit.) | 1.47 | 0.97 | 0.15 | 0.018 |
| Wt/pig wean (lbs.) | 12.7 | 13.5 | 0.02 | 0.24 |
| Wt gain/pig (lbs.) | 9.4 | 10.2 | 0.03 | 0.47 |
| Feed intake (lbs.) | 258 | 240 | 0.12 | 0.21 |
| Milk fat-d 1(%) | 4.9 | 6.9 | 0.01 | 0.41 |
| Milk fat-d 10(%) | 7.9 | 8.3 | 0.68 | 0.41 |
| Milk fat-d 21(%) | 6.8 | 6.3 | 0.17 | 0.81 |
| Days to first heat | 4.9 | 6.1 | 0.15 | 0.16 |
| Subsequent performance | | | | |
| litter (No.) | 10.0 | 10.2 | 0.84 | .041 |
| litter wt (lbs.) | 31.5 | 31.5 | 0.69 | 0.23 |
| Wean wt (lbs/pig) | 9.95 | 10.35 | 0.78 | |
| Days to pregnant | 7.1 | 10.1 | 0.12 | 0.21 |

Experiment 4

A longer term Ca-HMB feeding experiment was carried out with pregnant sows. The same ration was used as in Experiment 3, but different amounts of the

Ca-HMB were mixed with the ration to provide either 2 or 10 grams per 24 hours per sow.

In this experiment first parity sows were given either 0, 2 or 10 grams of Ca-HMB per day, and at approximately 45 days before farrowing all animals were started on these respective treatments. The treatments were fed during the prefarrowing period and were continued post farrowing until the piglets were weaned (about 3 weeks). Milk was collected as described for the Experiments 1 to 3. Sow body weight and back fat were not measured, and no adjustment for litter size or weight were made.

Table C

Effect of Feeding 2 or 10 Grams of Calcium-HMB to Sows During Gestation and Lactation and Resulting Piglet Performance

| Production | Dosage | | | P value | |
|---|---|---|---|---|---|
| Parameters | Control | 2g/d | 10g/d | C vs 2 | C vs 10 |
| Parity | 1 | 1 | 1 | | |
| No. Sows | 10 | 10 | 10 | | |
| Live born | 9.26 | 8.7 | 9.22 | .61 | .97 |
| Initial weight | 2.99 | 2.99 | 2.99 | (adjusted) | |
| Weight at 3 weeks | 11.8 | 12.2 | 13.4 | .66 | .12 |
| Gain/pig | 8.8 | 9.2 | 10.5 | .66 | .12 |
| Death % | 4% | 12% | 8% | .13 | .44 |

| | Control | 2g/d | 10g/d | C vs 2 | C vs 10 |
|---|---|---|---|---|---|
| Milk Composition (n=6 per treatment) | | | | | |
| Milk Fat % day 1 | 6.7 | 7.1 | 8.0 | .71 | .35 |
| Milk Fat % day 7 | 7.3 | 8.4 | 8.3 | .40 | .40 |
| Milk Fat % day 14 | 5.9 | 8.0 | 9.0 | .12 | .02 |
| Milk Fat % day 21 | 6.4 | 8.2 | 8.8 | .30 | .16 |
| Milk Protein % day 1 | 1.1 | 13.2 | 12.2 | .25 | .49 |
| Milk Protein % day 7 | 4.3 | 5.4 | 4.8 | .05 | .49 |
| Milk Protein % day 14 | 4.3 | 4.8 | 4.7 | .20 | .42 |
| Milk Protein % day 21 | 4.4 | 4.6 | 4.9 | .57 | .15 |

## Claims

I claim:

1. The method of increasing the nutritional value of colostrum and first milk of a pregnant mammal, comprising orally administering an HMB compound to said pregnant mammal for 24 to 72 hours before birth of the offspring, said HMB compound being β-hydroxy-β-methylbutyric acid in an edible form selected from (i) its free acid, or (ii) its sodium, potassium, magnesium, or calcium salt, or (iii) its methyl or ethyl ester, or (iv) its lactone (isovaleryl lactone), said HMB compound being administered in an amount effective for increasing the fat content of the colostrum and first milk of the mammal.

2. The method of claim 1 in which the oral administration of said HMB compound to said mammal is continued for 24 to 72 hours after the birth of the offspring.

3. The method of claim 1 in which said HMB compound is orally administered to said pregnant mammals in said effective amount for 30 to 60 days before the birth of the offspring.

4. The method of claim 1 in which the oral administration of said HMB compound to said mammal is continued after the birth of the offspring until the offspring is weaned.

5. The method of claims 1, 2, 3 or 4 in which said HMB compound is the calcium salt of β-hydroxy-β-methylbutyric acid (Ca-HMB).

6. The method of claims 1, 2, 3 or 4 in which said effective amount of said HMB compound is in the range of 0.5 to 100 milligrams HMB (Ca-HMB basis) per kilogram of body weight per 24 hours.

7. The method of claims 1, 2, 3 or 4 in which the offspring are being raised for meat production.

8. The method of claims 1, 2, 3 or 4 in which said pregnant mammal is a sow.

9. The method of increasing the nutritional value of colostrum and first milk of pregnant sows, comprising orally administering an HMB compound to said sows for 48 hours prior to birth of their offspring and continuing said oral administration for at least 48 hours after the birth of the offspring, said HMB compound being β-hydroxy-β-methylbutyric acid in an edible form selected from (i) its free acid, or (ii) its sodium, potassium, magnesium, or calcium salt, or (iii) its methyl or ethyl ester, or (iv) its lactone (isovaleryl lactone), said HMB compound being administered in an amount effective for increasing the fat content of the colostrum and first milk of said mammals.

10. The method of claim 9 in which said HMB compound is orally administered to said pregnant sows in said effective amount for 30 to 60 days before the birth of their offspring.

11. The method of claim 9 or 10 in which the oral administration of said HMB compound to said sows is continued after the birth of their offspring until the offspring are weaned.

12. The method of claims 1 or 9 in which said HMB compound is administered by mixing it with the feed being given to the mammals.

13. The method of claim 1 in which the offspring of said mammals are being raised for meat production and said mammals are cattle, sheep, goats or swine.

14. The method of claim 1 in which said mammal is a dog or cat.

15. The method of claims 9 or 10 in which said HMB compound is administered by mixing it with dry feed materials for said sows, and said feed materials are composed principally of ground corn, soybean meal, or mixtures thereof.

16. The method of claims 1, 2, 3 or 4 in which said pregnant mammal is a sow and said HMB compound is orally administered in an amount from .5 to 10 grams (Ca-HMB basis) per 24 hours.

17. The method of claim 1 in which said pregnant mammal is a cow and said HMB compound is orally administered in an amount of from 1 to 30 grams (Ca-HMB basis) per 24 hours.

18. The method of claim 1 in which said pregnant mammal is a ewe and said HMB compound is orally administered in an amount of from 0.5 to 10 grams (Ca-HMB basis) per 24 hours.

19. The method of claim 1 in which said pregnant mammal is a dog and said HMB compound is orally administered in an amount of from 10 to 2000 milligrams (Ca-HMB basis) per 24 hours.

20. The method of claim 1 in which said pregnant mammal is a cat and said HMB compound is orally administered in an amount of from 5 to 1000 milligrams (Ca-HMB basis) per 24 hours.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/01459

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :A23L 1/30; A61K 31/335, 31/19.
US CL :426/2; 514/449, 557.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 426/2; 514/449, 557.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US, A, 4,758,593 (NISSEN) 19 JULY 1988, ABSTRACT. | 1-20 |
| Y | US, A, 5,028,440 (NISSEN) 02 JULY 1991, COLUMN 1, LINES 38-41 AND 47-51 AND COLUMN 2, LINES 42-44. | 1-20 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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|---|---|
| Date of the actual completion of the international search<br>07 MARCH 1994 | Date of mailing of the international search report<br>04 MAY 1994 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>RAYMOND J. HENLEY III<br>Telephone No. (703) 308-1235 |

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